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PATENT, TRADEMARK
AND COPYRIGHT CAUSES
703-521-2110

September 9, 1980

REC'D SEP 10 1980

Noted
BAH

Susan A. Hutcheson
Philip Morris Research Center
P. O. Box 26583
Richmond, VA 23261

Re: U.S. Patent 4,155,909 and U.S. Patnet 4,220,781
Our References: D&O-77-8 and D&O-77-8/I

Dear Susan:

We have reviewed the possibly erroneous references to rearrangement and alkylation "according to the procedure described in Example 2" or "as in Example 2" in Examples 10 and 11, respectively, of the referenced patent specifications. The references are indeed in error. However, that error will not be corrected by referring back to "Example 3" instead of Example 2, as was suggested by the handwritten comment appearing on the telex copy which you provided us. Rather, reference must be made to one or both of the only two corresponding procedures that are described elsewhere in the examples -- Preparation III or Example 5. The comments of the inventors will be necessary to determine which procedure should be referred to.

The patent specifications disclose 2-alkyl nicotinoids and two general process schemes for their preparation. The specifications also disclose (but do not claim) intermediate products which are not useful in the preparation of 2-alkyl-nicotinoids. Examples 10 and 11 describe the preparation of compounds of this type. Furthermore, these compounds are produced by methods which are variations of the synthesis designated Scheme II in the specification. (The synthesis designated Scheme I is the subject of the claims of U.S. 4,220,781). More specifically, the variation is the substitution of sodium borohydride decyanation for acid hydrolysis in the "XIV → XV" step of Scheme II of the specification.

Examples 2, 4, 5, 10, and 11 and Preparations III and IV relate directly the process of Scheme II. Of these examples, only Examples 5 and Preparation III describe detailed methods for the [2,3] rearrangement of an α-cyanoamine and

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alkylation of the resulting rearranged intermediate product. In Example 11, the rearranged intermediate product is alkylated with a haloalkylnitrile, but in Example 10, the rearranged intermediate product is alkylated with benzylbromide. It may be assumed that, in terms of the alkylation step, the presence or absence of a cynano functional group in the haloalkyl alkylating reagent is not important. In both Preparation III and Example 5 the alkylating agent is a haloalkylnitrile (3-bromopropionitrile, the same one in Example 11).

The details of the alkylation steps of Preparation III and Example 5 differ although the general sequence of operations is the same. Reference to either or both of these examples in Examples 10 and 11 are appropriate in view of the foregoing, but the inventors must supply the proper approach.

It should be noted that deletion of Examples 10 and 11 would have no deleterious effect with respect to enablement of the claimed subject matter of either patent. The examples merely suggest the preparation of unclaimed intermediate compounds which are not generally useful in the preparation of nicotinoids except for the possibility that acid hydrolysis and hydrogenation of the product of Example 11 could produce 2-methylnornicotine.

The erroneous reference to Example 2 in Examples 10 and 11 would not therefore appear to affect the validity of the U.S. patents and it appears that appropriate correction could be made via a certificate of correction.

We will await your further instructions.

Very truly yours,

DEPAOLI & O'BRIEN

George A. Depaoli

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